Angiotensin-Neprilysin Inhibitor Therapy: A Retrospective Chart Study

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Abstract

Background: Guideline-directed medical therapy in patients with systolic heart failure (HF) has demonstrated improvement in morbidity and mortality rates. The FDA approved sacubitril/valsartan in 2015 to reduce the risk of cardiovascular death and hospitalization for HF. *Objective:* The purpose of this study was to evaluate the change in loop diuretic dose and the clinical outcomes of angiotensin receptor-neprilysin inhibitor (ARNI) therapy within a 90-day follow-up period. *Methods:* A retrospective chart review of 110 HF patients on concomitant ARNI and loop diuretic therapy at New York University Langone Health was conducted. The primary endpoint was a change in loop diuretic dose. Six secondary endpoints, including dose conversion from ACEi or ARB to ARNI therapy, were assessed. *Results:* Of the 110 HF patients, 72 did not receive diuretic dose adjustments, yet 40 (55.56%) experienced laboratory-dependent dehydration. Fifty-six percent of patients experienced an improvement in systolic blood pressure, and 52 percent experienced a decrease in diastolic blood pressure. Sixty percent of patients experienced an improvement in EF, with a median increase of 10.00% over a 90-day follow-up. A significant negative correlation between patients' age and absolute change in EF was identified ($r = -0.28$; $p < 0.05$), indicating that the increase in EF was stronger for younger patients. Eighteen hospitalizations occurred within a 90-day follow-up, with only 4 patients being admitted for heart failure exacerbation. *Conclusion and Relevance:* This study examines the real-world effects of ARNI therapy in patients with systolic heart failure. Optimization of HF medications, including ARNI therapy, remains an important factor for achieving the maximum benefits in heart failure management. ARNI therapy requires careful monitoring to ensure effective diuresis in symptomatic heart failure patients while avoiding adverse events. Future studies should address diuretic dose adjustment in conjunction with the administration of ARNI and sodium-glucose cotransporter-2 inhibitors.

Keywords: angiotensin receptor-neprilysin inhibitor; sacubitril; valsartan; loop diuretic; medication management; heart failure

Introduction

Heart disease continues to be the leading cause of death in the United States, accounting for one in every four deaths. Approximately 6.2 million adults have heart failure (HF), with nearly half at risk of dying within five years.[1] However, guideline-directed medical therapies (GDMT) can improve morbidity and mortality outcomes.

The 2017 American College of Cardiology, the American Heart Association, and the Heart Failure Society of America (ACC/AHA/HFSA) guidelines[2] recommend that patients with symptomatic heart failure with reduced ejection fraction (HFrEF) classified as NYHA class II or III, who can tolerate an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), to be switched to an angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan (Entresto®), for further morbidity and mortality reduction. This recommendation is based on the findings from the PARADIGM-HF trial.[3] Additionally, the 2022 ACC/AHA/HFSA guidelines emphasize that guideline-directed medical therapy for HFrEF should also include sodium-glucose cotransporter-2 (SGLT2) inhibitors.[4]

A post-hoc analysis of the PARADIGM-HF trial evaluated the furosemide dose and demonstrated a more considerable mean increase in the furosemide dose in the patient group that received enalapril compared to those who received sacubitril/valsartan (+21.7 mg versus +11.4 mg, respectively).[5] This analysis indicates that adjustments to the diuretic dose, particularly an increase in the furosemide dose, may not be necessary when used alongside ARNI therapy. This is likely due to the interaction between sacubitrilat, the active form of sacubitril, and valsartan, which inhibits the organic anion transporter 3 (OAT3). This interaction could lead to elevated levels of furosemide in the body, as furosemide is a substrate of OAT3.[5] Our study evaluated the real-world impact of ARNI therapy within a 90-day period, focusing on optimal medication titration and follow-up.

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Method

We conducted a retrospective chart review of HF patients at New York University Langone Health (NYULH) who were receiving concomitant therapy with an ARNI and loop diuretic therapy. Subjects were identified from the internal pharmacy database within the electronic health record (EPIC). The primary endpoint of the study was the change in loop diuretic

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dose. Secondary endpoints included: (a) dose conversion from ACEi or ARB to ARNI therapy, (b) incidence of dehydration during ARNI therapy, (c) change in renal function assessed by serum creatinine (SCr) and estimated glomerular filtration rates (eGFR), (d) change in blood pressures, (e) change in ejection fraction (EF), and (f) hospital admission rates.

Patients were included if they were initiated on ARNI therapy while receiving loop diuretic(s) for their heart failure symptoms in the outpatient setting. Exclusion criteria included a history of intolerance to ACEi, ARB, or ARNI, if they had NYHA Class IV HF, if they required inotropic therapy, or if ARNI therapy was initiated during hospitalization. Patients' demographics, comorbidities, laboratory data, and details of heart failure therapies (HF medications, doses, frequencies, and duration) were collected. In addition to the descriptive statistics used, we performed correlation analyses. We employed Pearson's correlation coefficient r, assessing the statistical significance of the observed correlation with a p-value threshold of less than 0.05.[6] The study received IRB approval from Long Island University's Office of Sponsored Research (IRB ID: B 18/11-184).

Results

Of a total of 400 subjects reviewed, 110 subjects were included in our analysis. Most patients were Caucasian males and former smokers, and more than half of patients had hypertension and hyperlipidemia. Notably, no patients in the study received bumetanide, and most received a beta-blocker, ACEi or ARB, and/or mineralocorticoid antagonist at the time of ARNI initiation (Table 1).

The majority of patients (72 patients; 65.45%) on ARNI therapy did not undergo a diuretic dose adjustment, whereas 17 patients (15.45%) received an increase, and 21 patients (19.09%) received a decrease in diuretic dose within the 90 days of ARNI initiation. When assessing ARNI initiation, it was found that 74.55% of patients maintained an equipotent dose change compared to baseline ACEi or ARB. Additionally, 13.64% of patients were prescribed a higher-than-recommended dose of ARNI therapy according to the package insert, while 11.82% received a lower dose.

We defined dehydration as a blood urea nitrogen (BUN) to SCr ratio greater than 20. We found that 56% of the patients who did not have their diuretic doses adjusted experienced dehydration at the 90-day follow-up. Additionally, among the 17 patients whose diuretic dose was increased, 10 patients (58.82%) also experienced dehydration. Specifically, the increases in diuretic doses were as follows: 1 patient had a 25% increase, 2 patients had a 33% increase, 6 patients experienced a 100% increase, and 1 patient had a 200% increase. Moreover, 11 out of 21 patients (52.38%) who had their diuretic doses decreased also experienced dehydration. In detail, 1 patient had a 29% decrease, 7 patients had a 50% decrease, and 3 patients discontinued the diuretic altogether (see Table 2).

In terms of changes in SCr levels, 8 patients (7.27%) exhibited no change. In contrast, 56 patients (50.91%) experienced an increase, with a median increase of 0.20 mg/dL, a mean increase of 0.23 mg/dL, and a standard deviation (SD) of 0.18. Additionally, 46 patients (41.82%) reported a decrease in SCr levels, with a median decrease of -0.11 mg/dL, a mean decrease of -0.13 mg/dL, and an SD of 0.10. Regarding the estimated glomerular filtration rate (eGFR), 13 patients (11.81%) had no change. Meanwhile, 50 patients (45.45%) saw an increase, with a median increase of 5.65 mL/min/1.73 m^2, a mean increase of 8.62 mL/min/1.73 m^2, and an SD of 7.60. Conversely, 47 patients (42.72%) experienced a decrease in eGFR, with a median decrease of -10.50 mL/min/1.73 m^2, a mean decrease of -11.99 mL/min/1.73 m^2, and an SD of 9.66.

In the study, 7 patients (6.36%) showed no change in systolic blood pressure (SBP). In contrast, 62 patients (56.56%) experienced a decrease in SBP, with a median decrease of -16.00 mmHg, a mean decrease of -19.34 mmHg, and an SD of 14.08. Meanwhile, 41 patients (37.27%) had an increase in SBP, with a median increase of 11.00 mmHg, a mean increase of 16.22 mmHg, and an SD of 15.60. Regarding diastolic blood pressure (DBP), 12 patients (10.91%) had no change. A total of 57 patients (51.82%) experienced a decrease in DBP, with a median decrease of -10.00 mmHg, a mean decrease of -11.88 mmHg, and an SD of 8.21. Additionally, 41 patients (37.27%) recorded an increase in DBP, with a median increase of 6.00 mmHg, a mean increase of 6.83 mmHg, and an SD of 3.99. No correlations were found between renal function, blood pressure, and the demographic characteristics of the patients.

Furthermore, we found that 66 patients (60.00%) experienced an improvement in their EF, with a median increase of 10.00%, a mean increase of 12.41%, and an SD of 9.83. This suggests that the efficacy of ARNI therapy can be observed within 90 days of treatment initiation. Meanwhile, 34 patients (30.91%) showed no change in their EF, and 10 patients (9.09%) experienced a decrease in their EF. We also assessed various correlations to explore associations between absolute changes in EF and patients' demographic characteristics. Notably, there was a significant negative correlation between patients' age and the absolute change in EF ($r = -0.28$; $p < 0.05$). This indicates that the increase in EF was less pronounced among older patients, suggesting that younger patients responded more positively to ARNI therapy in regard to EF.

Out of the 110 patients who received ARNI therapy, only 18 patients were admitted to the hospital within a 90-day follow-up period. Notably, only 4 of these admissions were related to heart failure exacerbations. Last, we did not identify any correlations between hospital admission rates and patients' demographic characteristics.

Discussion

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The PARADIGM-HF trial evaluated morbidity and mortality benefits of maximum doses of ARNI therapy (sacubitril/valsartan 97/103 mg twice daily) compared to enalapril (10 mg twice daily). The results indicate that patients benefit most from being on the maximum tolerated dose. In clinical practice, patients are often transitioned to an equipotent ARNI dose based on the prior ACEi or ARB dose. For patients without prior exposure to these medications, starting with a low dose of ARNI therapy (24/26 mg twice daily) and then increasing the dose to the maximum tolerated every 2 to 4 weeks is recommended. In our study, 74.55% of patients were initiated on the recommended ARNI doses; however, only 15 patients were titrated to the maximum ARNI dose of 97/103 mg twice daily within a 90-day follow-up period. We cannot rule out the possibility that if all patients could tolerate the treatment and were appropriately titrated to the maximum ARNI dose, the benefits observed in PARADIGM-HF could be replicated within the HF population of NYULH.

Our study's findings align with the results of the PARADIGM-HF trial. When evaluating diuretic dose adjustments, 65.45% of patients did not require changes within the 90-day follow-up. In contrast, a post-hoc analysis of diuretic use in PARADIGM-HF showed a larger mean increase in the furosemide dose in the enalapril group compared to the sacubitril/valsartan group,[4] and a median furosemide dose increased by +20 mg in the enalapril group.[5] While our study did not include a comparator group, there was no statistically significant difference in the diuretic dose changes from ARNI initiation to the 90-day follow-up. Among the 17 patients whose diuretic dose increased, we observed a mean increase of 28.24 mg with a median of 20.00 mg, as was similarly demonstrated in the enalapril group of this post-hoc analysis. This is likely due to the controlled environment within the trial, potentially signaling the importance of optimization of ARNI therapy in relation to diuretic requirement.

Ayalasomayajula et al. evaluated the pharmacokinetic /pharmacodynamic properties of furosemide when co-administered with ARNI in 24 healthy volunteers. They found a reduced maximum plasma concentration (Cmax) area under the concentration-time curve (AUC) and 24-hour urinary excretion of furosemide.[5] Although there was no difference in 24-hour diuresis, a reduction in 24-hour natriuresis was noted in that population.[5] While dehydration rates were not addressed in PARADIGM-HF or in the study by Ayalasomayajula et al., our research showed that 55.56% of subjects did not have a diuretic adjustment yet experienced dehydration at the 90-day follow-up. In contrast, 52.94% of patients with an increase in diuretic dose experienced dehydration, and 52.38% of patients with a decrease in diuretic dose also experienced dehydration. These findings suggest that evaluating loop diuretic doses, along with patient-specific clinical presentation, should be considered upon ARNI initiation to reduce the risk of dehydration within 90 days.

Regarding SCr, 56 patients in our study experienced a median increase of 0.20 mg/dL, while 46 patients experienced a median decrease of -0.11 mg/dL. With relation to the potential impact on eGFR as a marker of renal function, our study demonstrated a median increase of 5.65 mL/min/1.73 m^2 for 50 patients and a median decrease of -10.50 mL/min/1.73 m^2 for 47 patients within the 90-day follow-up period. A post-hoc analysis of the PARADIGM-HF trial focusing on renal function by Damman et al. demonstrated a lower rate of eGFR decline at -1.61 mL/min/1.73 m^2/year in the ARNI group compared to a -2.04 mL/min/1.73m^2/year in the enalapril group ($p < 0.001$).[7] In addition, a meta-analysis by Spannella et al. demonstrated a lower risk of renal dysfunction with ARNI compared to renin-angiotensin system (RAS) inhibitors alone (OR = 0.70; $p<0.001$).[8] Zhang et al.'s meta-analysis also demonstrated a lower risk of worsening renal function (RR 0.81, $P = 0.005$) but a higher risk of symptomatic hypotension (RR 1.47, $P < 0.001$) with ARNI compared to either enalapril or valsartan.[9] Due to the smaller patient sample size, shorter follow-up, and lack of a comparator group in our study, we cannot conclusively interpret the impact of ARNI on renal function.

Improvement in blood pressure resulting from ARNI therapy was observed in a post-hoc analysis of the PARADIGM-HF trial by Böhm et al., revealing a 4–6 mmHg reduction in SBP in the ARNI treatment group compared to the enalapril treated group.[10] Moreover, Ye et al. conducted a meta-analysis comparing ARNI dosages of 200 mg and 400 mg per day to olmesartan at 20 mg per day. They reported a weighted mean difference in the mean ambulatory SBP of -2.92 mmHg ($p<0.01$) for ARNI 200 mg and -4.36 mmHg ($p=0.02$) for ARNI 400 mg when compared to olmesartan.[11] Additionally, there was a statistically significant difference in mean ambulatory DBP with a weighted mean difference of -1.74 mmHg, $p<0.01$ for ARNI 200 mg and -2.62 mmHg, $p<0.01$ for ARNI 400 mg compared to olmesartan.[11]

In our study, 62 patients had an improvement in systolic blood pressure (SBP) with a median decrease in SBP of -16.00 mmHg (mean= -19.34, SD= 14.08). Twenty-six subjects experienced a drop in SBP of 20 mmHg or more. A similar improvement in diastolic blood pressure (DBP) was observed in 57 patients with a median decrease of -10.00 mmHg (mean= -11.88, SD= 8.21), and 32 subjects had a drop in DBP of 10 mmHg or more. Very few patients in our study experienced hypotension, defined as SBP < 90 mmHg or DBP < 60 mmHg. Specifically, four patients had a recorded BP reading of both SBP < 90 mmHg and DBP < 60 mmHg, while three patients had only a SBP reading of < 90 mmHg, with normal DBP, during the 90-day follow-up. Overall, our study demonstrates a potential for BP lowering, reinforcing the importance of closely monitoring this vulnerable population.

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In a post-hoc analysis of the PARADIGM-HF trial, Solomon et al. found that EF was a significant and independent predictor of cardiovascular outcomes with an increased risk associated with a decreased EF.[12] Specifically, for every 5-point reduction in EF, there was a 9% increased risk of cardiovascular death or hospitalization due to heart failure (HR: 1.09; p<0.001).[12] Data from a single center trial by Almufleh et al. demonstrated that ARNI therapy was associated with an average 5% ±1.2% increase in EF, rising from a mean baseline of 25.33% to 30.14% (p<0.001), with a median treatment duration of 3 months.[13] Additionally, in a prospective analysis of remodeling response, Martens et al. demonstrated an improvement in EF with a mean difference of 5.2% (p<0.001) from baseline, observed over a median follow-up period of 118 days (range: 77-160 days).[14]

In line with findings from these previous studies, we observed a significant increase in EF, albeit larger. Specifically, 66 subjects demonstrated an improvement in EF, with a mean increase of 12.41% and a median increase of 10.00% over the 90-day follow-up period. Additionally, we found a significant negative correlation between patients' age and the absolute change in EF ($r = -0.28$; $p < 0.05$), suggesting that younger patients may respond more favorably to ARNI therapy concerning EF. We also noted a low incidence of hospital admissions for acute decompensated heart failure.

Due to the retrospective nature of our study, several limitations may affect the interpretation of our results. These limitations include a relatively small sample size, a short follow-up period, the absence of an assessment of medication adherence, and a lack of a comparator group.[15] Moreover, our definition of dehydration was based solely on laboratory parameters and did not include clinical presentations to assess true volume status accurately. Lastly, we recognize that larger sample sizes can increase the statistical power of potentially significant correlations, and we encourage future studies to consider this limitation in interpreting our findings.[6]

In summary, our study emphasized the importance of optimizing ARNI therapy to the maximum tolerated dose to fully realize its benefits for heart failure patients. We also highlighted the need to evaluate diuresis and adjust diuretic dosages as necessary to prevent dehydration and its associated adverse effects, such as increased serum creatinine (Scr) levels and decreased estimated glomerular filtration rate (eGFR). Additionally, monitoring blood pressure is crucial to achieving target levels while avoiding hypotension. As noted in this study, we anticipate an increase in ejection fraction along with a reduction in hospital admissions, further supporting the inclusion of ARNI therapy in heart failure treatment regimens.

Conclusion

This study presents real-world outcomes regarding the recommended use of ARNI therapy in comparison to the usage observed in the PARADIGM-HF study. Our findings highlight the importance of careful monitoring and potential adjustments of diuretic doses when coadministering ARNI therapy. This is particularly essential since most treatment regimens will also include SGLT2 inhibitors. Such an approach ensures effective diuresis in symptomatic heart failure patients while preventing dehydration. Additionally, it is crucial to consistently monitor blood pressure and renal function to maximize treatment efficacy and avoid adverse events. An improvement in ejection fraction is expected; thus, starting ARNI treatment early and increasing the dose to the maximum tolerated level may help patients achieve optimal benefits for heart failure. In line with the 2022 ACC/AHA/HFSA guidelines for managing heart failure, future studies should explore the effects of adjusting diuretic doses when ARNI therapy is combined with sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Authors and Contributions: All authors contributed to the conception, design, analysis, and interpretation of the data presented. The third author contributed to the acquisition of data. All authors critically revised, gave final approval, and agree to be accountable for all aspects of work, ensuring integrity and accuracy of information presented within the manuscript.

Conflict of Interest: The authors declare that there are no conflicts of interest.

Ethics Statement: This study received an Institutional Review Board approval (review type: exempt) from Long Island University's Office of Sponsored Research (IRB ID: B 18/11-184).

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Table 1. Baseline Characteristics of the Retrospective Study

Baseline Characteristics	N=110
Age, years, median (IQR)	69 (61.3-79.8)
Male, n (%)	73 (66.4%)
Race, n (%)	
Caucasian	81 (73.6%)
African American	16 (14.5%)
Other	13 (11.8%)
Smoking History, n (%)	
Former	59 (53.6%)
Never	45 (40.9%)
Current	6 (5.4%)
Medical History, n (%)	
Hypertension	73 (66.4%)
Hyperlipidemia	56 (50.9%)
Coronary Artery Disease	53 (48.2%)
Atrial Fibrillation	50 (45.5%)
Diabetes	35 (31.8%)
Previous Myocardial Infarction	20 (18.2%)
Weight at Time of ARNI Initiation, kg, median (IQR)	81.6 (69.0-96.8)
SCr at Time of ARNI Initiation, mg/dL, median (IQR)	1.2 (0.9-1.4)
eGFR at Time of ARNI Initiation, mL/min/1.73 m2, median (IQR)	59.9 (46.5-71.2)
Left Ventricular Ejection Fraction, n (%)	
EF > 40%	7 (6.4%)
EF < 40%	103 (93.6%)
Median Daily Diuretic Doses, mg, (IQR)	
Furosemide	40 (20-40)
Torsemide	40 (20-80)
Medications at Time of ARNI Initiation, n (%)	
Diuretic	110 (100%)
Beta-blocker	105 (96%)
Angiotensin converting enzyme inhibitor	48 (44%)
Angiotensin receptor blocker	34 (31%)
Mineralocorticoid antagonist	58 (53%)
Digoxin	22 (20%)

ARNI: Angiotensin receptor-neprilysin inhibitor

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Table 2. Summary of Observed Findings

Primary Endpoint, n (%)*			
Increased diuretic dose	17 (15.45%)		
Decreased diuretic dose	21 (19.09%)		
No change in diuretic dose	72 (65.45%)		
Secondary Endpoints	Diuretic Adjustment**		
	Increase	Decrease	No Change
Hospital Admission within 90 days, n (%)	5 (29.41%)	4 (19.05%)	9 (12.50%)
Hypotension (SBP/DBP), n^	2/3	1/2	4/8
Dehydration, n (%)	10 (58.82%)	11 (52.38%)	40 (55.56%)
Reasons for Hospital Admission, n	Increase	Decrease	No Change
Acute HF exacerbation	2	0	2
NSTEMI	0	1	0
ICD placement/revision	0	1	5
Other	3	2	2
Final ARNI Dose, n	Increase	Decrease	No Change
24/26 mg BID	10	13	29
49/51 mg BID	5	6	27
97/103 mg BID	2	1	12

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ARNI: Angiotensin receptor-neprilysin inhibitor
* No statistical differences were noted from baseline to 90-day follow-up
**Percentages based on total number of patients with respective diuretic adjustments as noted in the primary endpoint
^Hypotension defined as either SBP < 90 mmHg or DBP < 60 mmHg or both

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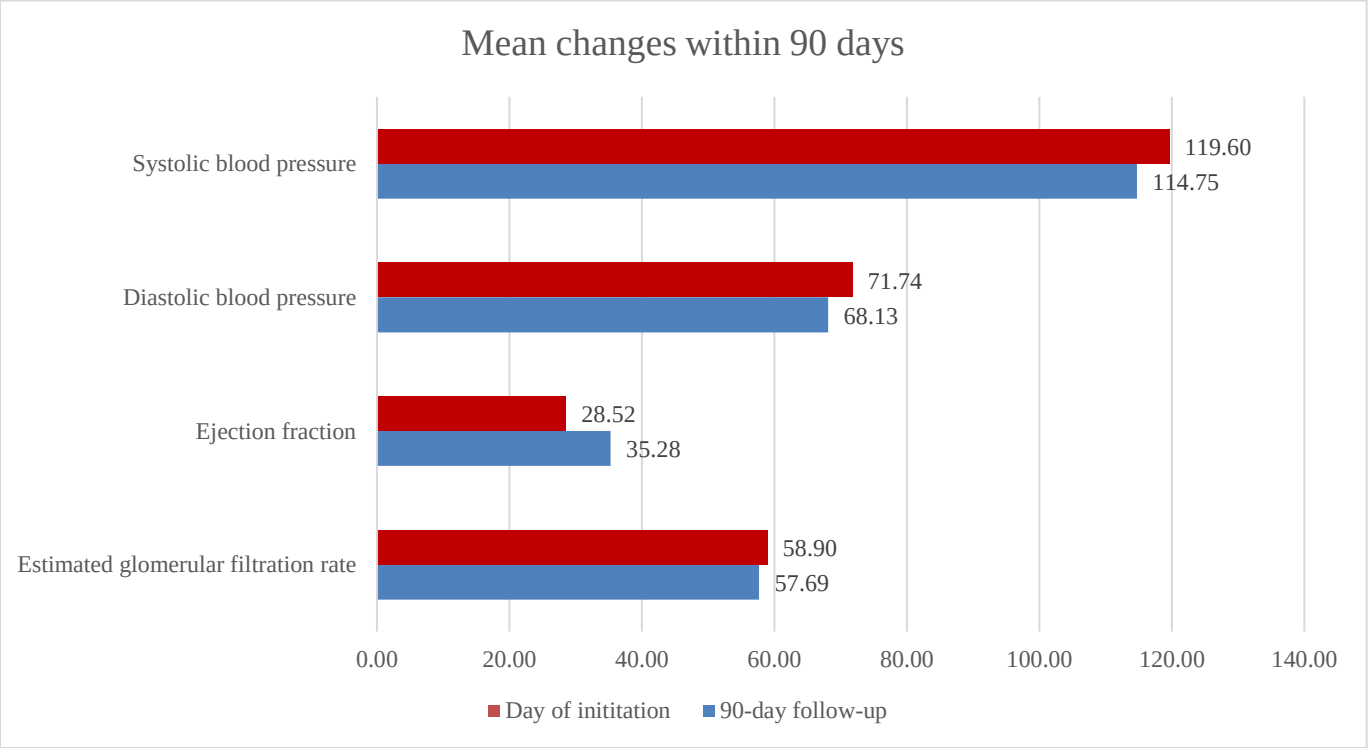
Figure 1. Mean Value Changes within 90 Days of Initiation



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